Neonatal Death Suspected To Be From Sepsis Was Found To Be Kernicterus With G6PD Deficiency

abstract

We cared for a term male infant born to Burmese immigrants. At about 24 hours a total serum bilirubin (TSB) was 9.3 mg/dL, and phototherapy was begun. It was stopped 48 hours later, with a TSB of 10.9 mg/dL, and he was discharged from the hospital with an appointment for a repeat TSB check 48 hours later. A few hours before the appointment he became listless and apneic, and his parents took him to the emergency department of the regional children's hospital, where sepsis was suspected. The TSB was 41 mg/dL. He died 4 hours later, despite intensive care efforts, with opisthotonus and refractory hypotension. Blood drawn before the exchange transfusion had low glucose-6-phosphate dehydrogenase (G6PD) enzymatic activity, and sequencing of the G6PD gene revealed the G6PD Mahidol mutation (c.487G>A). Cultures and postmortem examination did not demonstrate an infectious process, but kernicterus was present. Acute kernicterus can mimic septic shock. Pediatrics 2013;132: e1694–e1698

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ABBREVIATIONS

G6PD—glucose-6-phosphate dehydrogenase
TSB—total serum bilirubin

Dr Christensen drafted the manuscript and organized the data; Dr Yaish contributed to the design of the report, including the blood film, and was critically involved in writing the manuscript; Dr Wiedmeier helped draft the initial manuscript and organize the data; Dr Reading supervised the G6PD and UGT1A1 gene sequencing and provided essential guidance in writing the case report; Dr Pysher provided all data from the postmortem examination and wrote critical portions of the manuscript related to the pathology; Dr Palmer wrote critical portions of the manuscript; Dr Prchal provided critical advice on the writing of the manuscript; and all authors approved the final manuscript as submitted.

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Efforts to prevent kernicterus include the American Academy of Pediatrics guidelines for management of hyperbilirubinemia. Recent reports, including those from our health care system (Intermountain Healthcare in the western United States) indicate that cases of extreme hyperbilirubinemia and kernicterus are still occurring. We now report a tragic case where death from kernicterus occurred in a term newborn who was not recognized to be at high risk for kernicterus and where the illness that led to hospitalization on day of life 5 was thought to be sepsis. The autopsy showed kernicterus with no evidence of infection, and gene sequencing of DNA obtained from blood drawn before the exchange transfusion showed glucose-6-phosphate dehydrogenase (G6PD) deficiency due to the Mahidol mutation.

CASE

The patient was born at 39 weeks’ and 2 days’ gestation to a non-consanguineous Burmese couple who immigrated to the United States 2 years earlier. Mother’s blood type was O+. Neither parents, siblings, nor extended family members had a history of jaundice, anemia, or gallstones. Prenatal care, labor, and vaginal delivery were all normal. Birth weight was 3290 g (45th percentile), length 53 cm (88th percentile), and occipitofrontal circumference 36 cm (85th percentile). Apgar scores were 9 and 9 at 1 and 5 minutes. He was cared for in the well-baby nursery and was breast fed and supplemented with Similac 20 kcal/oz formula.

He appeared well and at 23 hours had a total serum bilirubin (TSB) of 9.3 mg/dL (>95th percentile on the hour-specific bilirubin nomogram). Phototherapy was begun using a Giraffe Spot PT Lite (Ohmeda Medical, Laurel, MD) with a measured irradiance of 30 μW/cm²/nm at 38 cm (15 inches) from the skin. The baby’s blood type was B+, and the direct antiglobulin test (Coombs test) was negative. TSB testing was repeated at the following times: 39 hr (11.7 mg/dL), 43 hr (11.1 mg/dL), 47 hr (10.6 mg/dL), and 67 hr (10.1 mg/dL). At that time phototherapy was discontinued. At 73 hr the TSB had increased only to 10.9 mg/dL, the hematocrit was 55.2%, and he was discharged from the hospital. With the assistance of a translator (parents spoke the language Karen) an appointment was made for an office visit in 48 hours, where a repeat TSB would be obtained.

He fed well at home and appeared healthy, but in the afternoon just before the scheduled return visit (120 hours after birth) he became lethargic and would not breastfeed, and his respiration was irregular. Therefore, the parents took him to the hospital emergency department, where intermittent apnea, opisthotonic posturing, and marked jaundice were observed. Bag and mask ventilation were initiated, followed by endotracheal intubation. He was admitted to the hospital for intensive care and antibiotic administration for what was thought to be septic shock.

On admission he appeared well hydrated, weighing 3210 g (97% of birth weight). The TSB was 41 mg/dL. While he was prepared for an exchange transfusion, phototherapy was provided and ampicillin and cefotaxime administered after blood, tracheal, and spinal fluid cultures were obtained. A parenteral dose of albumin (1 g/kg) and an infusion of intravenous immunoglobulin (750 mg/kg) were given. His capillary pH was 7.49, PO₂ 32 mm Hg, and PO₂ 73 mm Hg. Blood lactate was slightly elevated (2.7 mmol/L). Over the next hour he needed ever-higher FiO₂, reaching 100% before the exchange transfusion began. At that time inhaled nitric oxide at 20 ppm was started, with no improvement. Hypotension was treated with crystalloid boluses and dopamine and epinephrine drips.

Before the exchange transfusion his hematocrit was 36.5%, hemoglobin 12.2 g/dL, mean cell volume 103.1 fl, red cell distribution width 15.5%, and reticulocyte count 6.0%. The platelet count was 282 × 10⁹/L and mean platelet volume 10.9 fl. The urine was positive for hemoglobin. His blood smear (Fig 1) revealed normocytic, normochromic erythrocytes, occasional spherocytes, rare nucleated red blood cells, and polychromasia. Many schistocytes, bite cells, and blister cells were seen. Echinocytes were also noted. The neutrophils and monocytes appeared normal, with no toxic granulation or Dohle bodies. No primitive or immature cells were observed.

About 1.5 hours after the exchange transfusion began, bradycardia followed by asystole occurred. Serial monitoring of serum electrolyte and glucose values revealed no abnormalities. Despite resuscitative efforts, he died about 4 hours after arrival at the hospital. Blood obtained before the exchange transfusion suggested G6PD deficiency, with 2.7 U G6PD enzymatic activity per gram of hemoglobin (normal, 7.0–20.5 U/g). DNA was extracted from blood drawn before the exchange transfusion. Full-gene sequence analysis of the G6PD gene revealed a single point mutation in exon 395x124 to 547x236.
6, G6PD c.487G>A, resulting in a glycine to serine amino acid substitution at position G6PD p.163. This substitution is well described among Southeast Asian populations and is known as G6PD Mahidol. It results in a marked reduction in G6PD activity and has been associated with severe neonatal jaundice and kernicterus. The UGT1A1 gene was sequenced and revealed a wild-type (TA)₆ repeat in the promoter, so UGT1A1 polymorphism did not augment the severe hyperbilirubinemia in this neonate.

Postmortem examination revealed bilateral symmetric bright yellow discoloration of deep gray nuclei, including the thalami, basal ganglia, and hippocampi, and of the floor of the fourth ventricle, inferior olivary nuclei, cerebral peduncles, and choroid plexus at the foramina of Luschka (Fig 2). There was an incidental cavum septum pel- lucidum. In addition to moderate staining of the skin, there was marked icterus of the sclerae, oral mucosa, subcutaneous tissues, serous effusions, lymph nodes, and renal collecting system. There were no dysmorphic features. Histologic examination of the brain showed yellow discoloration of neurons in several areas (lateral thalami, subiculum, nucleus of cranial nerve III, adjacent to the fourth ventricle, and internal granular layer of cerebellum). There was no evidence of infection, inflammation, or hemorrhage. Bilirubin staining was noted in exfoliated epithelial cells in the lungs and macrophages in lymph nodes. The liver showed normal architecture and development, moderate fine vacuolization of hepatocytes, and sinusoidal erythropoiesis.

DISCUSSION

G6PD deficiency is the most common enzyme deficiency in humans, with an estimated 400 million people affected worldwide.⁶ It is a well-known cause of severe neonatal jaundice; 21% (26/125) of neonates listed in the USA Kernicterus Registry had G6PD deficiency recognized.⁷,⁸ More than 400 variants have been identified in the G6PD gene (OMIM #305900), located at Xq28, with consequences to affected neonates ranging from extremely mild to very severe. Because G6PD is in the hexose monophosphate pathway, which is the only nicotinamide adenine dinucleotide phosphate-generating process in mature erythrocytes, deficiency can lead to hemolytic jaundice.⁶,⁹

Our case serves as a reminder of unresolved questions related to G6PD deficiency and severe neonatal jaundice: Why are neonates with G6PD deficiency at risk for kernicterus? Why does acute bilirubin encephalopathy sometimes present like septic shock? Should newborn metabolic screens include G6PD deficiency?²

Why Are Neonates With G6PD Deficiency at Risk for Kernicterus?

Acute hemolysis can occur in neonates with G6PD deficiency exposed to certain oxidant substances such as sulfonamide products, methylene blue, or naphthalene.⁶,⁹⁻¹¹ After the death of this neonate, we sought possible explanations for his acute rise in TSB from 10.9 to 41 mg/dL in <48 hours. We learned that the parents dressed him in clothing obtained from Deseret Industries, a used clothing store. We contacted the store management to inquire about policies and were told that only donated swimsuits and underclothes were washed before being sold; other items, specifically baby clothes and receiving blankets, were not. Thus, it is possible that the donated items had been stored near mothballs containing naphthalene. No medications, home remedies, henna, or other oxidative stressors were identified by interview with the family. Because his clothes and blanket were cremated with his remains, according to parental directive, the suspicion that naphthalene was the trigger remains unproven.

The G-to-A change at base G6PD c.487 (exon 6) in G6PD Mahidol leads to substitution of serine for glycine at amino acid G6PD p.163. This mutation results in class 2 enzyme derangement (World Health Organization classification). Matsuoka et al¹² found that 11% of blood samples from people in remote areas of Myanmar (formerly Burma) indicated G6PD deficiency, and Iwai et al¹³ reported that >90% of G6PD variants in the Burmese population are G6PD Mahidol. G6PD variants are believed to provide a selective survival advantage in humans in regard to Plasmodium vivax and Plasmodium falciparum malaria. A recent study demonstrated that G6PD Mahidol has been under strong and recent positive selection over the past 1500 years, reducing P vivax, but not P falciparum, parasite density.¹⁴

Why Does Acute Bilirubin Encephalopathy Sometimes Present Like Sepsis?

As detailed by AlOtabi et al,¹⁵ neurologic manifestations of acute bilirubin encephalopathy include lethargy, hypotonia, thermal instability, and apnea, features also typical of neonatal sepsis. Hameed et al¹⁶ reported 162 neonates admitted to hospitals in Baghdad for management of hyperbilirubinemia; 18 (11%) died with acute bilirubin encephalopathy. Similarly, Manning et al¹⁷ reported 16 neonates from the United Kingdom and Ireland admitted to hospitals with acute bilirubin encephalopathy.
of whom 3 died. Neurologic deterioration in acute kernicterus accompanies neuronal necrosis, somewhat similar to that seen with hypoxia and ischemia. Clearly, when a 5-day-old presents to an emergency department with lethargy, apnea, and jaundice, infection should be a prime consideration. However, acute bilirubin encephalopathy should also be recognized as a possibility and the "crash-cart approach" described by Hansen instituted, including emergency intensive phototherapy during preparation for exchange transfusion.

Should Newborn Metabolic Screens Include G6PD Deficiency?

Kaplan and Hammerman issued the caution that kernicterus associated with G6PD deficiency is not just a problem in the Far and Middle East but occurs in North America as well. The topic of routine neonatal screening for early detection of G6PD deficiency was recently reviewed by Watchko et al. They concluded that no national consensus has emerged about the need for newborn G6PD screening in the United States. One question raised in their discussion was whether knowledge of G6PD deficiency in the immediate newborn period would alter neonatal outcome. In the present case we speculate that it could have, in at least 2 ways. First, at the time of hospital discharge, had the pediatrician realized this neonate had G6PD deficiency he would probably have requested TSB follow-up <48 hours after discharge. Second, with the knowledge that the neonate had G6PD deficiency, the pediatrician could have cautioned the parents about washing baby clothing and blankets that might have had contact with mothballs. Moreover, had the physicians in the emergency department known this neonate had G6PD deficiency, the presentation with apnea, lethargy, and jaundice might have more quickly prompted the "crash-cart approach" to phototherapy. Even without knowing this patient had G6PD deficiency, his physicians might have averted this tragedy by paying careful attention to the bilirubin levels and the response to phototherapy. First, a TSB of 9.3 mg/dL at age 23 hours is well above the 95th percentile. A TSB this high in the first day should always be considered the result of hemolysis until proven otherwise. Second, the poor response to phototherapy suggests hemolysis is present. Third, neonates with hemolytic jaundice are much more likely to develop a significant rebound after stopping phototherapy. For these reasons it would have been appropriate to obtain an outpatient TSB check no later than 1 day after hospital discharge.

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